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YOUNG & THOMPSON
209 Madison Street
Suite 500
ALEXANDRIA, VA 22314

EXAMINER	
TON, THAIAN N	
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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 09/980,484
Filing Date: March 25, 2002
Appellant(s): HATZFELD ET AL.

Philip Dubois
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 29, 2008 appealing from the Office action mailed March 27, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Hatzfeld *et al.* (**Exp. Hematology**, 25(8): 777, Abstract #174, 1997)

Fortunel *et al.* (**J. of Cell Science**, 111: 1867-1875, 1998).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 9, 11, 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzfeld *et al.* (**Exp. Hematology**, 25(8): 777, Abstract #174, 1997) when taken with Fortunel *et al.* (**J. of Cell Science**, 111: 1867-1875, 1998).

Hatzfeld teach that endogenous or added TGF-β down-modulates various cytokine receptors, and that this effect can be suppressed within 6 hours by the addition of anti-TGF-β antibodies, or antisense nucleotides. Hatzfeld study the release from TGF-β growth inhibition of high proliferative potential-quiescent primitive progenitors to understand whether this inhibitor is a central regulator of the stem cell compartment. They teach that these observations are used in developing an *in vitro* assay which combines receptor induction by anti-TGF-β together with optimal cytokine stimulation which can be performed using non

purified hematopoietic progenitors. They teach that this method can render quiescent primitive progenitors responsive to optimal combinations of cytokines to improve the *in vitro* expansion of clinical samples. They teach the neutralization of an inhibitor of cell development (i.e., TGF-β). They further teach using these methods on CD34+ cells.

Hatzfeld *et al.* differ from the claimed invention, in that they do not teach specific amounts of added TGF-β or specific amounts of anti-TGFβ that are required in the claims. However, prior to the time of the claimed invention, Fortunel *et al.* teach culturing CD34+ stem cells with 2 or 5 ng/ml of TGFβ and 5μg/ml of anti-TGFβ blocking antibody (see page 1868, col. 1-2, Hematopoietic growth factors and antibody). They teach that anti-TGF β releases the cells from quiescence, thus allowing them to divide (see Abstract). They teach amounts of TGFβ which are within the range required by claims. They teach culturing cells, which falls within the claimed range of 1 to about 10^{10} cells per ml, as the term "cells" encompasses at least one cell, as required by the claims. Additionally, with regard to repeatedly practicing the methods steps, or repeat administration, as recited by the claims, this step encompasses, for example, changing the media, which contains both TGFβ and anti-TGFβ, which is taught by Fortunel (p. 1869, 2nd col., 1st full ¶). Given that the methods require the same cell types and reagents that are taught by both Hatzfeld and Fortunel, the methods would necessarily result in the maintenance of the cells in a non-differentiated state. There is no specific requirement in the claims for the amount of time that the cells need to be maintained in a non-differentiated state, therefore, the combined art provides sufficient motivation and teachings to arrive at the claimed invention. Finally, specific method steps, such as "returning the cells to a resting state by treatment of the cells with an inhibitor" (claim 34, step(b)) would necessarily occur when performing the methods taught by the combined art, because the methods of art provide the same method steps and reagents, which would predictably result in the requirements of the claims.

Thus, given the combined teachings of Hatzfeld *et al.* and Fortunel *et al.*, it would be obvious for one of skill in the art to use the specific ranges, as taught by Fortunel *et al.*, for use in the assay, as taught by Hatzfeld *et al.*, with a reasonable expectation of success. One of ordinary skill would have been motivated use the specific ranges, as taught by Fortunel they show that the anti-TGFβ blocking antibody effectively neutralizes exogenously added TGFβ, (p. 1868, 2nd col., 1st ¶), and they suggest using TGFβ/ anti-TGFβ in an assay detect quiescent progenitor cells (HPP-Q cells) (p. 1870-71, bridging ¶), the same assay suggested by Hatzfeld *et al.*.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

(10) Response to Argument

Appellants' Arguments. Appellants argue that there is no suggestion of using the teachings of the Hatzfeld abstract to provide a process that would maintain a non-differentiated state of human stem cells, while allowing cell division of the stem cells. Appellants argue that although Fortunel teach a method that could be used to study not only human quiescent progenitors, but other somatic stem cell systems, and that there is no suggestion of maintaining a non-differentiated state of human stem cells, while allowing cell division of said human stem cells (pp. 4-5 of the Brief).

Appellants further argue that the proposed combination of the references fails to render the claimed invention obvious, because Hatzfeld focuses primarily on the effect of TGFβ/ anti-TGFβ on various receptors, and more particularly pertains to the use of anti-TGFβ for rendering quiescent hematopoietic progenitors sensitive to cytokine stimulation. Appellants argue that the Hatzfeld abstract does not suggest how human stem cells can be multiplied in vitro while being maintained in a non-differentiated state, or the beneficial effect obtained by adding an inhibitor of

cell development, such as TGFβ, for maintaining a "stem" state during cell divisions. Additionally, Appellants argue that Hatzfeld does not teach how to use TGFβ/ anti-TGFβ in a sequential combination or cyclically, and that it is believed that the skilled artisan would be deterred by Hatzfeld from using TGFβ/ anti-TGFβ to multiply non-differentiated stem cells, since Hatzfeld teach the possibility of using "transient activation of HPPQ" as "an excellent tool to mark stem cells and follow their development", which suggests pushing the cells towards further differentiation, instead of maintaining the cells in a non-differentiated state. See p. 5 of the Brief.

Response to Arguments. Appellants' argument that the HPPQ assay used in Hatzfeld suggests its use in studying differentiation for stem cells, rather than for maintaining them in a non-differentiated state is not persuasive. MPEP §2105 states that, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." The specification teaches that the HPP-Q test, "allows for the verification that the inhibitor of cell development, in particular, TGF-β, is maintaining the stem cells, in particular hematopoietic stem cells, at rest." See p. 12, lines 18-20. Thus, the as-filed specification clearly teaches that this assay is used to evaluate maintenance of HSCs at rest. This is clearly supported by Hatzfeld *et al.*, who state that this test can be used for the expansion of HSCs (see Abstract, last ¶) and by Fortunel *et al.*, who teach utilizing the HPPQ test to identify HPPQ cells as, "primitive progenitors for which very low concentrations of TGF-β1 can down-modulate receptors controlling their cycling status. When a quiescent stem/progenitor cell is activates, it maintains for a few division its immature phenotype and its high proliferative potential. ... Similarly, we have evidence that even after activation, HPP-Q cells maintain for at least one division their ability to return to the quiescent state in

response to physiological concentrations of TGF-β1." See p. 1872, 2nd col., 1st ¶. Thus, both Hatzfeld and Fortunel teach that the HPPQ assay is designed to test for cells that are able to divide but also maintain their primitive stem cell status. Additionally, the term "sequentially" is interpreted to mean application of one factor and then the second factor; in the instant case TGFβ/ anti-TGFβ, which is clearly taught by the combined art. Additionally it is noted that Hatzfeld teach that the HPPQ assay renders quiescent HSCs responsive to cytokines which can improve the expansion of the cells. See last ¶. They further suggest that using their HPPQ assays, either non-purified or purified progenitor cells can be cultured, for either short term or long-term use, such as clinical expansion of the cells. Thus, even though the cited art does not explicitly state that the methods are used to maintain a non-differentiated state of human stem cells while allowing for cell division, the art certainly teaches using their methods in maintaining cells in a primitive state and to allow them to divide. Furthermore, because both Hatzfeld and Fortunel teach the same reagents, cells and method steps as the claimed invention, this would necessarily maintain the cells in a non-differentiated state, because all that is required by the claims is taught or suggested by the prior art. Therefore, the Examiner maintains that the combined art provides sufficient motivation and teachings to arrive at the claimed invention.

Appellants' Arguments. Appellants argue that both the disclosure of Hatzfeld and Fortunel are, at best, cumulative to what is already disclosed in the present Application and both pieces of art are both directed to using the HPPQ assay, which was used to evaluate the differentiation potential of stem cells. Appellants argue that the HPP-Q assay is also distinguishable from the claimed invention in that the assay utilizes very short term proliferation of cells that grow as colonies in semi-solid medium, which is not suitable for carrying out the multiplication of stem cells without differentiation, as recited in the claimed invention. See page 7 of the Brief.

Response to Arguments. With regard to Appellants' arguments that the HPPQ assay is further distinguishable from the claimed invention in that the assay utilizes a very short term proliferation of cells that grow as colonies in semi-solid medium, which is not suitable for carrying of the multiplication of stem cells without differentiation, as recited by the claims, it is noted that Appellants are arguing limitations that are not found within the claims. There is no time frame required by the claims that distinguish from the assays taught by the combined art. The claims simply require maintaining a non-differentiated state of HSCs, while allowing for cell division of the cells, by allowing cells to divide until they reach a particular, pre-determined number (see claim 1, line 9). Similarly, claim 33 only recites the production of a "predetermined number" of cells (lines 9-10). The pre-determined number is not recited in the claim, and therefore encompasses any number of cells. Thus, because Hatzfeld teach that one could use this assay with either non-purified progenitors in semi-solid culture, **or** highly purified progenitors in long-term liquid culture to characterize and phenotype the stem cell compartment, and Hatzfeld disclose the same, the Examiner maintains that the combined teachings of Hatzfeld and Fortunel provide sufficient guidance and motivation to arrive the claimed invention, with a reasonable expectation of success.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Thaian N. Ton/
Primary Examiner
Art Unit 1632

Conferees:

/Peter Paras, Jr./
Peter Paras, Jr.
SPE Art Unit 1632

/Ram R. Shukla/
Ram R. Shukla
Supervisory Patent Examiner, Art Unit 1634